Spotlight on hormones in Systemic Lupus Erythematosus

By

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Systemic Lupus Erythematosus

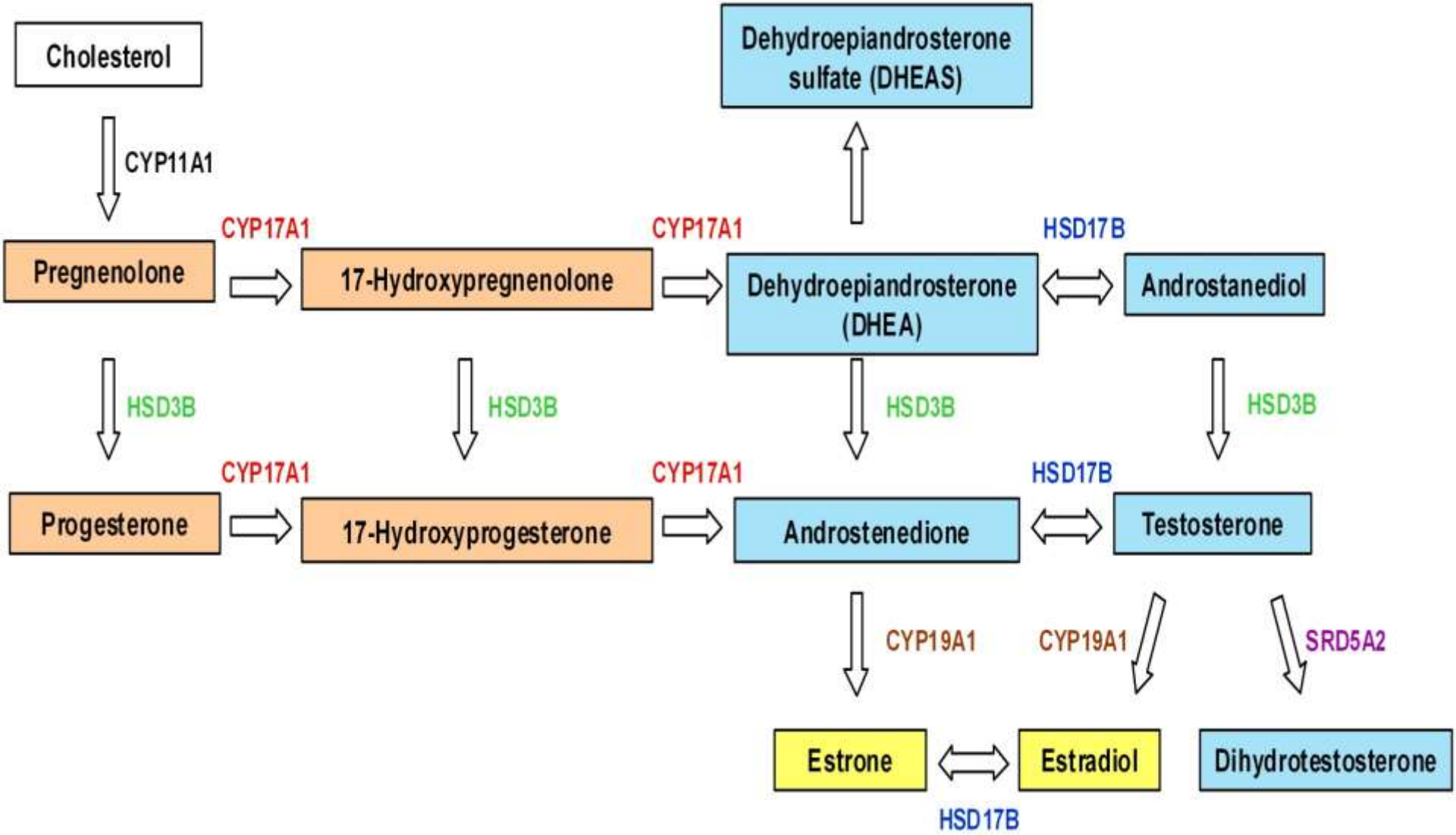
A chronic inflammatory systemic autoimmune disease of unknown etiology characterized by polyclonal B-cell activation and abnormal autoantibodies

The role of hormones in the pathogenesis of SLE.

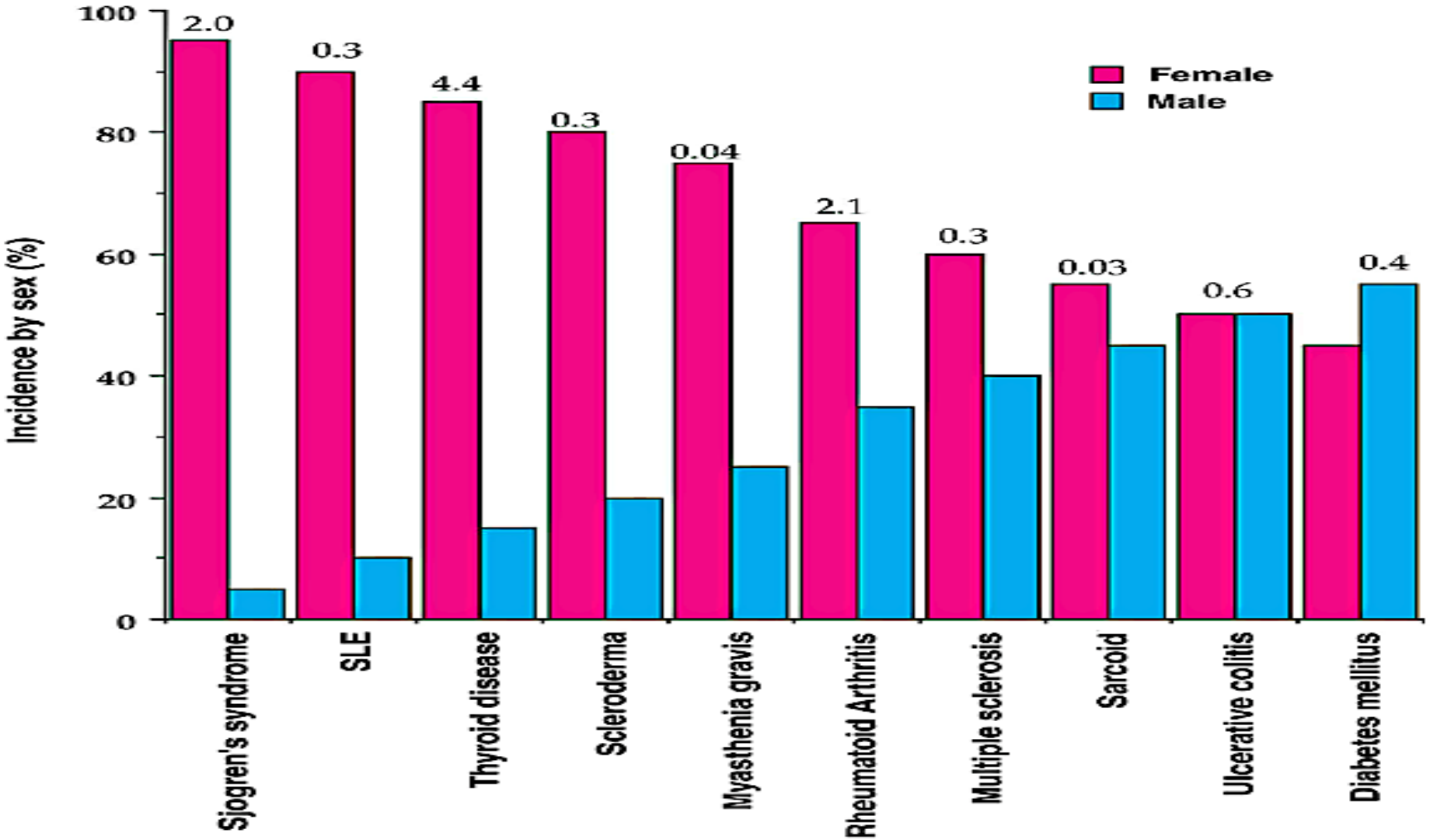
- Hormones may not have a direct causative role in SLE, but a milieu consisting of different values of hypothalamo–pituitary and gonadal hormones may create an endogenous environment for susceptible individuals to develop the disease.
- Changes in the concentrations of sex steroids, coupled with certain yet undiscovered environmental factors, may lead to disease flares and serve to explain the “wax and wane” nature of the disease.

Sex hormones and SLE

Sex hormones



Prevalence of autoimmune diseases by sex.



- The increased female-to-male ratio of SLE patients suggests that sex factors modulate disease proclivity and development
- Also increase in SLE incidence following puberty and almost a complete reversal of disease following menopause .
- Pregnancy is associated with exacerbation of SLE patients

Table 6. Sex hormone changes in SLE patients*

Hormone	Women	Men
DHEA/DHEAS	↓	Probably ↓
↓		
Progesterone	↓	Unknown
↓		
Testosterone	↓	Normal
↓		
Estradiol	↑	Normal
↓ (stimulates)	↑	↑
Prolactin		

Serum 17β-estradiol in SLE

- Estradiol is the most potent and predominant estrogen in serum, is the aromatized end-product of the gonadal steroid metabolic pathway.
- patients with SLE showed significantly increased serum estradiol concentrations
- One study demonstrated lower estradiol levels in SLE patients compared with controls.

Serum 17β-estradiol in SLE

Table 1. Controlled studies of serum 17β-estradiol concentrations in patients with systemic lupus erythematosus*

Authors, year (ref.)	Subjects	Conclusions
Female-only studies		
Jungers et al, 1983 (30)	19 SLE/12 controls	No significant difference
Feher et al, 1987 (31)	4–7 SLE/4–10 controls; 22 SLE/11 controls	No significant difference (regardless of cyclicity or menopause)
Lahita et al, 1987 (32)	12 SLE/pooled controls	No significant difference
Arnalich et al, 1992 (33)	26 SLE/21 controls	No significant difference
Folomeev et al, 1992 (34)	9 SLE/4 controls	No significant difference; aromatase activity varied inversely with SLE disease activity and positively with estradiol; no difference in female and male aromatase activity
Cheng and Li, 1993 (35)	140 SLE/20 controls	E_2 significantly higher in SLE; lupus activity related to incremental E_2 concentrations
Munoz et al, 1994 (36)	14 SLE/20 controls, premenopausal; 8 SLE/8 controls, postmenopausal	E_2 significantly lower in SLE; serum E_2 inversely related to disease activity at specific menstrual cycle stages; alterations in intermediate E_2 metabolism in SLE patients
Verthelyi et al, 2001 (37)	75 SLE/38 controls, premenopausal; 45 SLE/20 controls, postmenopausal	E_2 significantly higher in SLE (before or after menopause); cytokine imbalances did not correlate with hormone concentrations
Male-only studies		
Mackworth-Young et al, 1983 (38)	9 SLE/11 controls	No significant difference
Miller et al, 1983 (39)	49 SLE/49 controls	E_2 significantly higher in SLE; 18 of 49 had abnormally high E_2 concentrations
Carrabba et al, 1985 (40)	10 SLE/10 controls	No significant difference; lower testosterone/estradiol ratios in SLE men
Lavalle et al, 1987 (41)	8 SLE/11 controls	E_2 significantly lower in SLE
Folomeev et al, 1992 (34)	6 SLE/4 controls	No significant difference; trend toward increased E_2 and aromatase activity levels in SLE patients; however, aromatase activity varies inversely with SLE disease activity
Sequeira et al, 1993 (42)	14 SLE/17 controls	No significant difference
Cheng and Li, 1993 (35)	19 SLE/7 controls	E_2 significantly higher in SLE
Munoz et al, 1994 (36)	5 SLE/7 controls	No significant difference
Vilarinho and Costallat, 1998 (44)	7 SLE/10 controls	E_2 significantly lower in SLE
Chang et al, 1999 (43)	16 SLE/20 controls	No significant difference
Mok and Lau, 2000 (45)	35 SLE/33 controls	No significant difference
Verthelyi et al, 2001 (37)	8 SLE/28 controls	E_2 significantly higher in SLE; serum cytokine imbalances did not correlate with hormone concentrations

* SLE = systemic lupus erythematosus; E_2 = 17β-estradiol.

Serum 17β-estradiol in SLE

- Possible explanations for elevated estrogen level in lupus females include increased activity of aromatic hydroxylase or increased production of LH driving testosterone aromatization.
- Inflammatory cytokine action increasing LH release from the pituitary gland, increasing aromatization, and making estradiol a surrogate marker of inflammation rather than a modulator of disease activity.

Serum 17β-estradiol in SLE

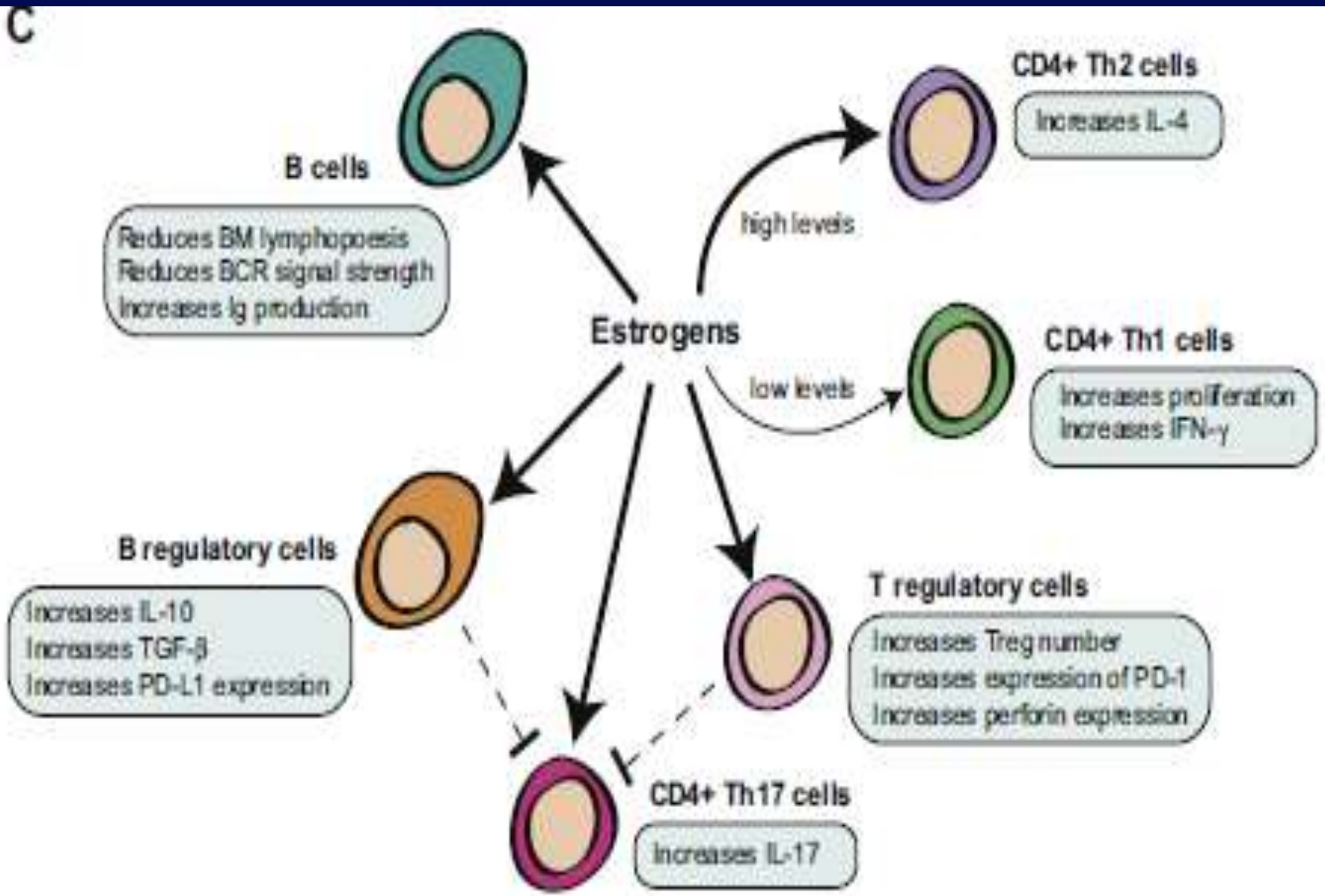
- SLE patients have higher levels of cytochrome p450 enzymes CYP1B1 and CYP1A1, resulting in the conversion of estradiol into one of the most potent and feminising oestrogens, 16α-hydroxyesterone.

Effects of estrogen on immune system

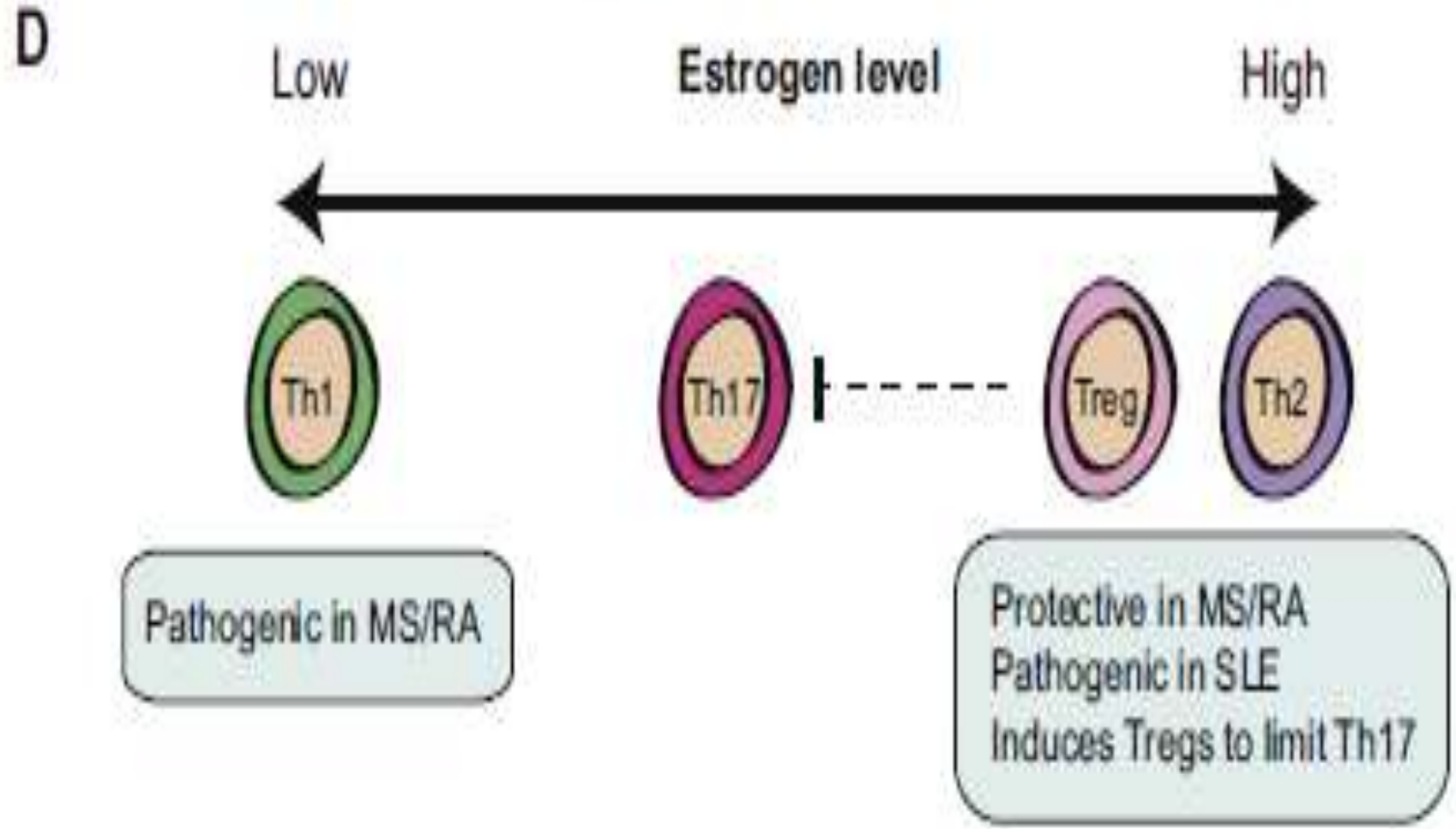
- Both physiological and supraphysiological concentrations of oestrogens facilitate humoral responses, leading to increased B cell proliferation and antibody production. On the contrary, high doses of oestrogens inhibit T cell responses, such as proliferation and IL-2 production.

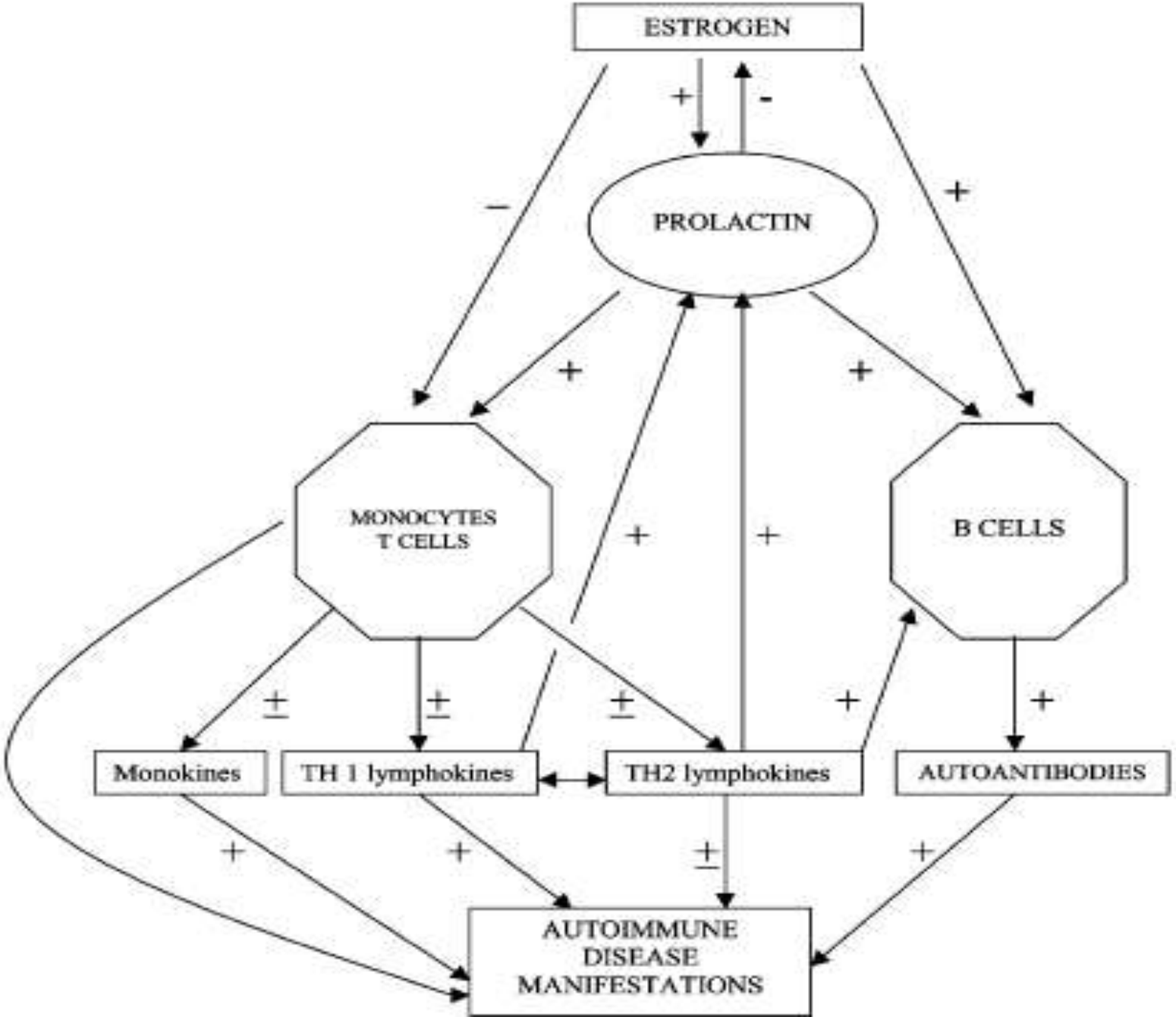
- Estrogens may aggravate SLE by prolonging the survival of autoimmune cells, increasing T helper type 2 (Th2) cytokine production, and stimulating B cells to produce autoantibodies. The inhibition of the Th1 response and the enhancement of CD40L expression on lupus T cells may indirectly promote the Th2 response and lead to further B cell hyperactivity.

Estrogen and immune system



Estrogen level and autoimmune diseases




ESTROGEN
+
-
PROLACTIN
−
+
+
+
MONOCYTES
T CELLS
B CELLS
+
+
±
±
±
+
+
Monokines
TH 1 lymphokines
TH2 lymphokines
AUTOANTIBODIES
+
+
±
+
AUTOIMMUNE
DISEASE
MANIFESTATIONS

SLE and contraception

- Because of this hormonal connection, women with SLE need to be very careful about hormonal contraceptive use and hormone replacement therapy. Birth control issues, namely a proper understanding of contraceptive options, are very important in women with lupus, as unwanted pregnancy can result in health risks to the mother and fetus.

SLE and contraception

- However, recent studies have shown that OC use actually doesn't increase the risk of serious lupus flare, time to first flare, or global disease activity, in women with mild disease. Because of these studies, birth control pills with lower doses of estrogen are likely safe in women with mild lupus, but should be avoided in women at increased risk of clotting, or in women with moderate or severe lupus.

SLE and contraception

- Because progestin -only OC's don't confer the increased risk of clotting events that estrogen-containing pills do, they may be safer options in women with lupus and a tendency for clotting events. However, progestin-only pills are associated with breakthrough bleeding and a higher failure rate than combination pills. These pills also need to be taken at the same time every day without a pill free interval.

SLE and contraception

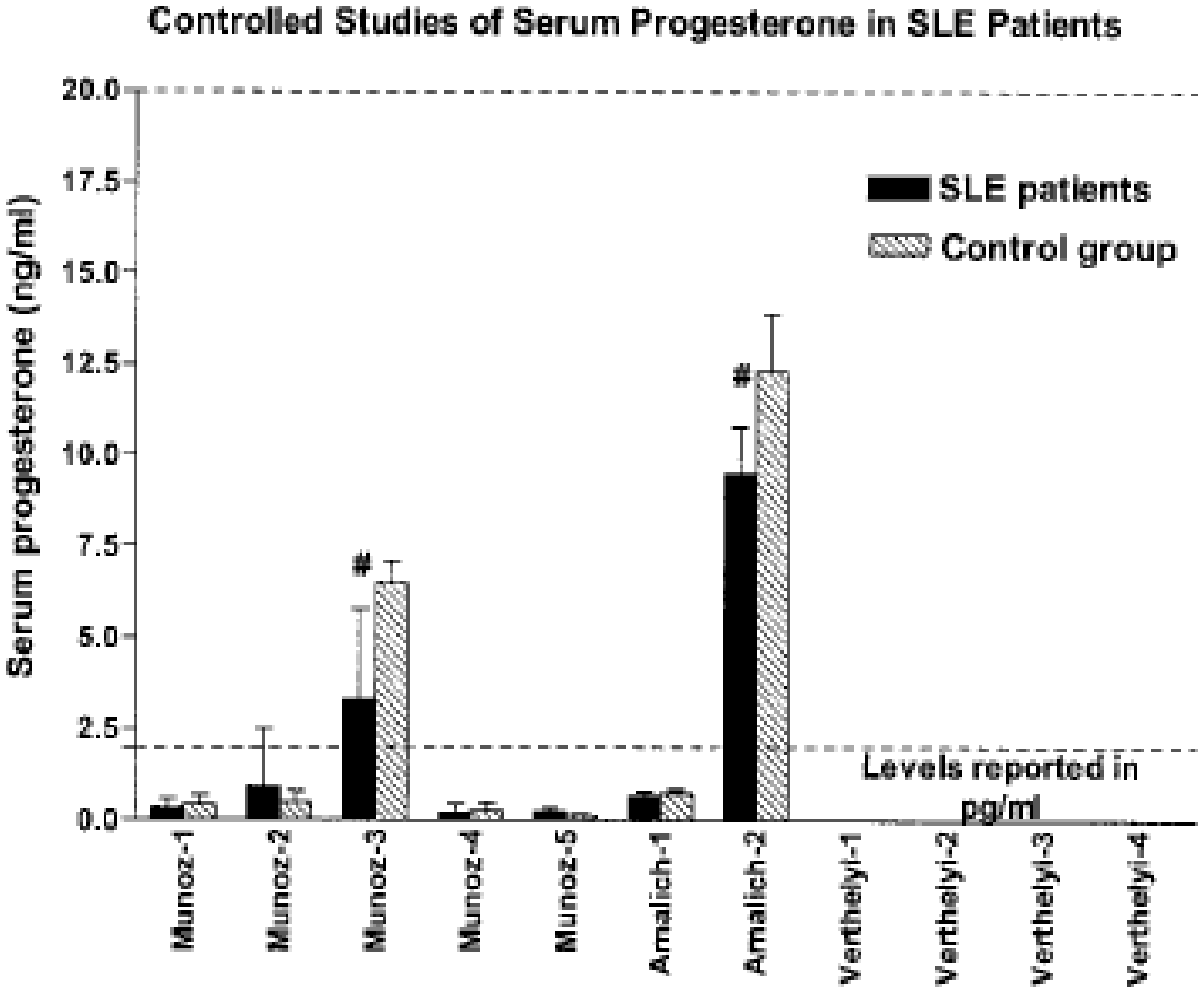
- Other contraceptive options include Depo-Provera (DMPA, a progestin that is injected intramuscularly and results in effective contraception for 3-4 months), Implanon (a single rod progestin implant that is inserted resulting in effective contraception for 3 years), and Intrauterine devices.

Tamoxifen and SLE

- Therapeutic administration of estrogen receptor blockade with tamoxifen does not improve and may exacerbate SLE disease activity (sturgess et al.,1984). Hence, a clear understanding of relationships between serum estradiol concentrations, steroid enzymes, metabolite effects, and disease activity in SLE remains elusive.

Serum progesterone

- Progesterone is an upstream precursor of testosterone and estradiol.
- Progesterone concentrations have been shown to be lower in SLE patients compared with healthy controls,
- Although only one study took into account menstrual cycles, during which progesterone levels were markedly lower during the follicular phase than during the luteal phase.


Controlled Studies of Serum Progesterone in SLE Patients
Serum progesterone (ng/ml)
20.0
17.5
15.0
12.5
10.0
7.5
5.0
2.5
0.0
SLE patients
Control group
Levels reported in pg/ml
#
#
Munoz-1
Munoz-2
Munoz-3
Munoz-4
Munoz-5
Amalich-1
Amalich-2
Verthelyi-1
Verthelyi-2
Verthelyi-3
Verthelyi-4

Serum testosterone

- Testosterone, the immediate precursor of estradiol, is found in both men and women and is generally accepted as being immunosuppressive.
- Female-only SLE studies showed significantly decreased testosterone in patients with SLE compared with controls

- Low plasma testosterone, might be explained by increased testosterone oxidation at C-17 or increased tissue aromatase activity. The concentrations of androgens correlate inversely with disease activity.

Table 3. Controlled studies of serum testosterone in SLE patients*

Authors, year (ref.)	Subjects	Conclusions
Female-only studies		
Jungers et al, 1982 (60)	13 SLE/12 controls	Testosterone significantly lower
Jungers et al, 1983 (30)	19 SLE/12 controls	Testosterone significantly lower
Feher et al, 1987 (31)	54 SLE/44 controls	Testosterone significantly lower
Lahita et al, 1987 (32)	22 SLE/pooled controls	No significant difference; all androgen levels lower in SLE patients compared with controls, but not always statistically significant; androgens inversely correlated with disease activity
Arnalich et al, 1992 (33)	26 SLE/21 controls	No significant difference
Folomeev et al, 1992 (34)	9 SLE/4 controls	Testosterone significantly lower
Cheng and Li, 1993 (35)	140 SLE/20 controls	Testosterone significantly lower; decrements inversely proportional to lupus activity
Munoz et al, 1994 (36)	14 SLE/20 controls	No significant difference
Male-only studies		
Stahl and Decker, 1978 (61)	12 SLE/31 controls	No significant difference; hypogonadism or androgen deficiency not evident
Mackworth-Young et al, 1983 (38)	9 SLE/11 controls	Testosterone significantly lower; testosterone lower in SLE patients but not different from other chronic diseases
Carrabba et al, 1985 (40)	10 SLE/10 controls	No significant difference; lower testosterone/estradiol ratios in SLE men
Lavalle et al, 1987 (41)	8 SLE/11 controls	Testosterone significantly lower
Folomeev et al, 1992 (34)	6 SLE/4 controls	Testosterone significantly lower
Sequeira et al, 1993 (42)	14 SLE/17 controls	No significant difference
Cheng and Li, 1993 (35)	19 SLE/7 controls	Testosterone significantly lower; inversely related to disease activity
Munoz et al, 1994 (36)	5 SLE/7 controls	No significant difference
Vilarinho and Costallat, 1998 (44)	7 SLE/10 controls	No significant difference
Chang et al, 1999 (43)	16 SLE/20 controls	No significant difference
Mok and Lau, 2000 (45)	33 SLE/35 controls	No significant difference

* SLE = systemic lupus erythematosus.

- SLE clinical improvement with testosterone administration, is documented
- In addition, patients with Klinefelter's syndrome, characterised by hypergonadotrophic hypogonadism, are prone to the development of SLE.[7]

Serum DHEA/DHEAS

- DHEA is a hormone naturally produced by the adrenal gland and is converted into sex hormones. DHEA is also present in the Mexican yam, from which it is extracted for use as a nutritional supplement (Coates 2010).
- DHEA-s blood levels be kept between 350 – 490 µg/dL for men and 275 – 400 µg/dL for women in order to achieve optimal immunomodulatory action.

- Low levels of DHEA-s, a plentiful metabolite of DHEA in humans, have been observed in patients with lupus and other inflammatory diseases (Sawalha 2008). DHEA and its various metabolites exert considerable influence over immune system activity by regulating production of multiple cytokines including IL-2, IL-1, IL-6 and TNFα (Sawalha 2008).

- In a clinical trial, when individuals with lupus took 200 mg of DHEA daily for 24 weeks, the lupus flares was significantly reduced (Chang 2002). Also, reduced blood levels of the cytokine IL-10, which enhances antibody production (Chang 2004). This reduction in IL-10 may have contributed to the reduced incidence of lupus flares.
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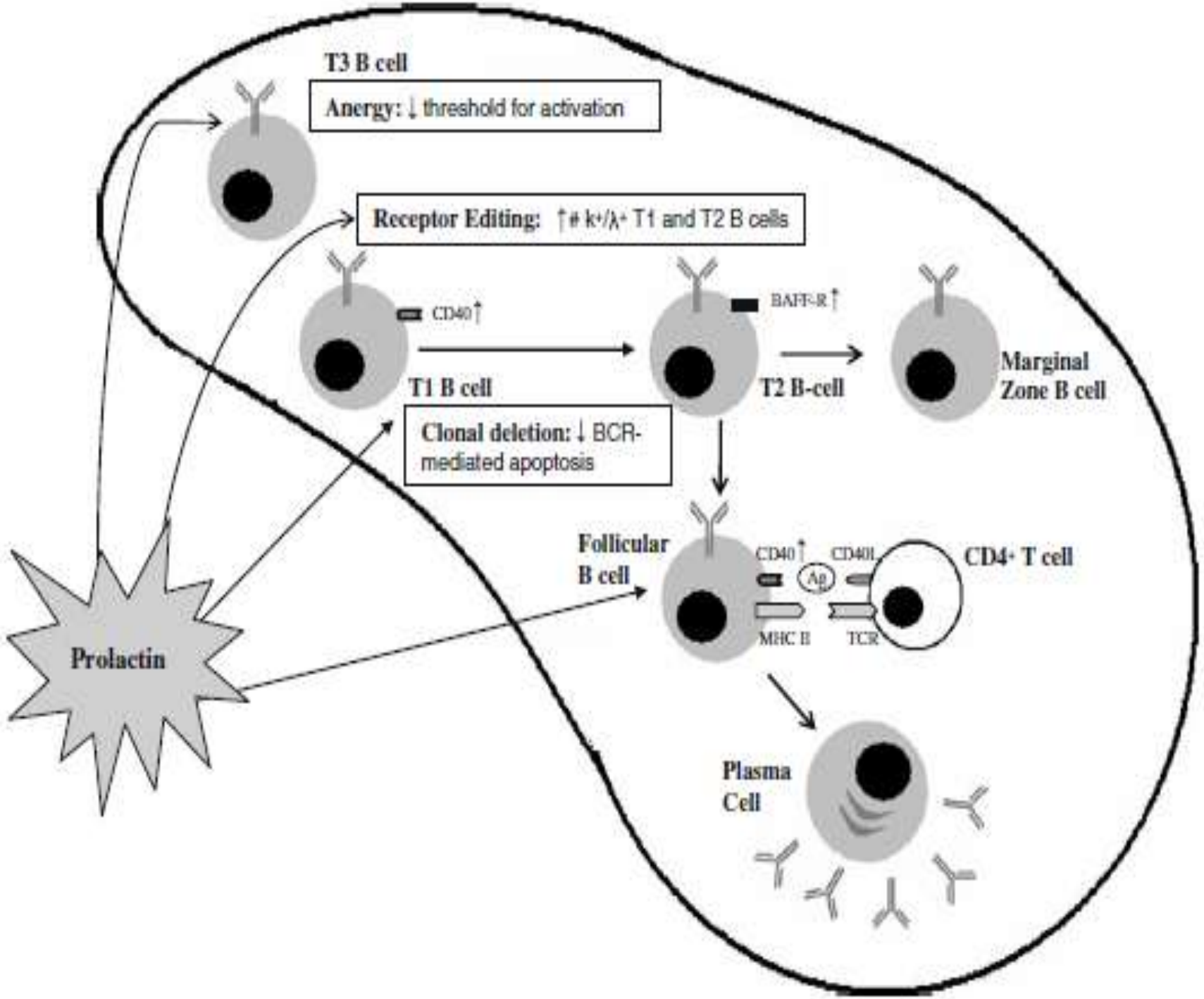
- Another double-blind, randomized, controlled trial involving 41 women found that six months treatment with 20 – 30 mg DHEA daily improved mental and emotional well-being in lupus patients (Nordmark 2005). Also, at a dose of 200 mg daily, DHEA improved bone mineral density in postmenopausal women with lupus (Hartkamp 2004).

Serum prolactin

- Prolactin has been found to be an immunostimulatory hormone. The main origin is the anterior pituitary, but lymphocytes are also capable of producing prolactin, which serves as an autocrine or paracrine mediator. Chronic hyperprolactinaemia induced by syngeneic pituitary gland implantation stimulates primary humoral antibody responses in rats, and accelerates autoimmune phenomena in lupus prone mice.


T3 B cell
Anergy: ↓ threshold for activation
Receptor Editing: ↑# κ+/λ+ T1 and T2 B cells
CD40↑
T1 B cell
BAFF-R↑
T2 B-cell
Marginal Zone B cell
Clonal deletion: ↓ BCR-mediated apoptosis
Follicular B cell
CD40↑
CD40L
Ag
MHC II
TCR
CD4+ T cell
Prolactin
Plasma Cell

- The prolactin has receptors beyond the reproductive axis including immune cells, and it is thought to promote autoimmunity in human and murine lupus.
- Induced hyperprolactinemia exacerbates disease activity and leads to premature death.
- Persistent mild–moderate hyperprolactinemia alters the selection of the naïve B cell repertoire.

- Prolactin impairs all three mechanisms of B cell tolerance induction (negative selection, receptor editing, and anergy) and thereby contributes to the pathogenesis of autoimmunity.
- The effects of prolactin are genetically determined as shown by the differential response to the hormone in the different mice strains.

- Recent data suggest that the stimulatory actions of estrogens on autoreactive B cells require the presence of prolactin.

- Hyperprolactinaemia has been demonstrated in a proportion of patients with SLE of both sexes. Prolactin concentrations correlate with disease activity in some studies. Bromocriptine, a dopamine agonist that selectively inhibits prolactin secretion from the pituitary, has been shown to be useful in the treatment of non-life threatening SLE. However, the exact role of prolactin in SLE requires further work because a positive correlation between lupus activity and prolactin values cannot be demonstrated consistently.

Table 5. Prevalence of hyperprolactinemia in SLE patients and controls*

Author(s), year (ref.)	Serum hyperprolactinemia	
	Patients	Controls
Jara et al, 1992 (71)	10/45 (22)	0/28 (0)
Sequeira et al, 1993 (42)	0/14 (0)	0/13 (0)
Pauzner et al, 1994 (82)	16/82 (20)	ND
Buskila et al, 1996 (83)	10/63 (16)	ND
Formiga et al, 1996 (84)	6/20 (30)	ND
Neidhart, 1996 (72)	9/29 (30)	ND
Ostendorf et al, 1996 (85)	4/182 (2)	ND
Huang and Chou, 1997 (73)	12/30 (40)	2/20 (10)
Mok et al, 1997 (79)	25/72 (31)	ND
Rovensky et al, 1997 (77)	11/34 (31)	ND
Alvarez-Nemegyei et al, 1998 (93)	30/66 (45)	ND
Ferreira et al, 1998 (74)	9/24 (38)	2/15 (13)
Jimena et al, 1998 (76)	10/36 (28)	ND
Mok et al, 1998 (80)	4/13 (13)	ND
Vilarinho and Costallat, 1998 (44)	2/7 (29)	ND
Mok and Lau, 2000 (81)	0/35 (0)	0/33 (0)
Jacobi et al, 2001 (78)	17/60 (28)	0/47 (0)
Leanos-Miranda et al, 2001 (86)	41/259 (16)	ND
Pacilio et al, 2001 (87)	21/78 (27)	ND
Total†	237/1,149 (21)	4/156 (3)

Table 4. Controlled studies of serum prolactin concentrations in SLE*

Author(s), year (ref.)	Subjects	Conclusions
Female studies		
Arnalich et al, 1992 (33)	26 SLE/21 controls	No significant difference
Jara et al, 1992 (71)	45 SLE/28 controls	Prolactin significantly increased; correlation with SLE disease activity; subset of patients were hyperprolactinemic
Munoz et al, 1994 (36)	14 SLE/20 controls; 8 SLE/8 controls	Prolactin significantly decreased (compared with controls at certain stages of the menstrual cycle)
Neidhart, 1996 (72)	29 SLE/29 controls	Prolactin significantly increased; increased prolactin associated with increased cortisol; significant correlation between serum prolactin and anti–double-stranded DNA
Huang and Chou, 1997 (73)	30 SLE/20 controls	Prolactin significantly increased
Rovensky et al, 1997 (77)	26 SLE/19 controls	Prolactin significantly increased
Ferreira et al, 1998 (74)	24 SLE/15 controls	Prolactin significantly increased
Gutierrez et al, 1998 (75)	10 SLE/10 controls	No significant difference
Jimena et al, 1998 (76)	36 SLE/20 controls	Prolactin significantly increased; no correlation found between prolactin levels and disease activity
Jacobi et al, 2001 (78)	60 SLE/47 controls	Prolactin significantly increased; correlation with lupus disease activity
Male studies		
Lavalle et al, 1987 (41)	8 SLE/11 controls	Prolactin significantly increased
Munoz et al, 1994 (36)	5 SLE/7 controls	No significant difference
Vilarinho and Costallat, 1998 (44)	7 SLE/10 controls	No significant difference
Chang et al, 1999 (43)	16 SLE/20 controls	Prolactin significantly increased

* SLE = systemic lupus erythematosus.

Prolactin in SLE

- The little PRL (23 kDa) was demonstrated to be related with lupus activity while macroprolactinemia or low levels of little PRL were negatively related to the SLEDAI score . The immune complexes of PRL-anti-PRL (which are the macroprolactins) are not biologically active, since the large size disturbs the cross through the capillary walls to reach the target tissues.
- The free HPRL is related to neurological, renal, and hematological involvement, serositis, anti-double stranded DNA (dsDNA) and hypocomplementemia

Prolactin in SLE

- The presence of anti-PRL antibodies in the serum of lupus patients was found to correlate with decreased disease activity. This effect is explained by attenuation of the biological activity of PRL, by interfering with binding to the PRL-Rs on lymphocytes. The anti-PRL antibodies may deregulate PRL secretion and induce HPRL

Bromocriptine and SLE

- Inhibition of PRL secretion by bromocriptine decreased serum anti-dsDNA antibody titers and improved the survival of lupus-prone mice.
- The effect of bromocriptine was through induction of natural nonspecific CD8+ suppressor cells .
- Bromocriptine therapy for SLE patients suffering from mild to moderate active disease was beneficial with significant improvement in activity scores.
- Bromocriptine reduced the flare rate and discontinuation of bromocriptine was followed by a flare of disease activity in all patients

Serum prolactin concentrations in female patients with Systemic lupus erythmatosus

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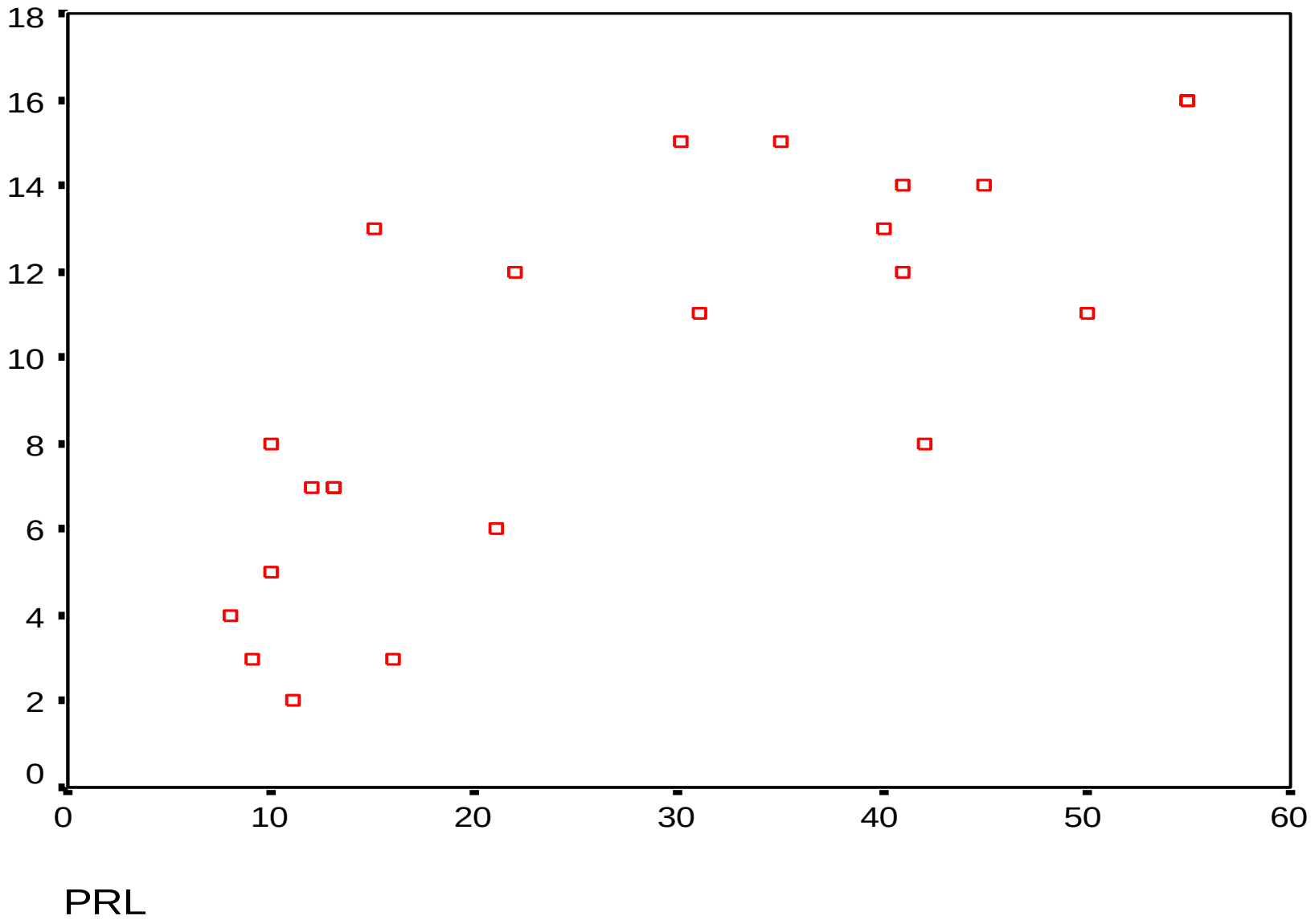
Aim of The Work

- To assess the frequency of hyperprolactinemia in patients with SLE and evaluate its possible clinical significance with the disease activity.


RESULTS

Results

- Elevated serum concentrations of PRL > 20 ng/ml were found 10/23 (43%) of patients with SLE.
- The mean prolactin levels was 27.1±16.1 SD ng/ml (range 8-55).
- There were no significant correlation between the age of patients, disease duration and their serum mean PRL levels (p= 0.8, 0.3 respectively).



P < 0.001, r = 0.7.

Conclusions

- In the present study mild to moderate elevated PRL levels were found in 10/23 (43%) of patients with SLE.
- Hyperprolactinemia detected by IRMA was associated with disease activity in SLE .
- Additional studies will clarify the possible role of PRL and its isoform in regulation of immune responses and clinical expression in SLE.

Indications for sella MRI in SLE

- Prolactinomas are rare in SLE patients with no consistency of the clinical manifestations of HPRL or in the coincidence of HPRL with flares of SLE disease activity
- **Prolactin level > 100 ng/ml**
- **Nervous manifestations**
- **Amenorrhea galactorrhea resistant to treatment**

Gonadotrophin releasing hormone (GnRH)

- GnRH, a decapeptide produced by the hypothalamus, regulates the release of LH and follicle stimulating hormone from the anterior pituitary. Recent animal studies show that GnRH is immunostimulatory. In lupus prone mice, GnRH has been shown to exacerbate lupus, but the effect appears to be sexually dimorphic. However, the role of GnRH in human SLE requires further evaluation.

The hypothalamo–pituitary–adrenal (HPA) axis

- HPA axis is the chief component of the stress system. The stress induced increase in serum concentrations of glucocorticoids is essential for the prevention of autoreactive or unrestrained amplification of the immune response, which results in self injury and autoimmunity. A defective HPA axis may confer susceptibility to autoimmune disorders. Female Lewis (LEW/N) rats, characterised by a defective hypothalamic corticotrophin releasing hormone (CRH) response to several immunological activators, including IL-1, are highly susceptible to a wide variety of experimental autoimmune disorders.

- Studies on the function of the HPA axis in patients with SLE are limited and often confounded by the effect of concomitant glucocorticoid treatment. A study on a group of active untreated female patients with SLE reports that the cortisol response to induced hypoglycaemia is significantly lower in patients than in healthy controls, indicating that some degree of HPA axis dysfunction does exist. The dysregulated HPA axis in SLE may be responsible for disease susceptibility and progression.

SLE and endocrinal diseases

Hyperglycemia in SLE

- Types of hyperglycemia in SLE includes pre-diabetes and diabetes (type 1DM, type 2 DM and steroid induced DM)
- SLE patients with hyperglycemia were characterized by insulin resistance and reduced pancreatic beta cell function.
- Old age and high glucocorticoid doses were risk factors for hyperglycemia in SLE patients.

Hyperglycemia in SLE

- The prevalence of diabetes mellitus and impaired glucose tolerance are quite high in SLE patients (31.5%)(15% diabetic and 17% pre-diabetes). It is suggested that plasma glucose concentration should be monitored regularly and oral glucose tolerance test should be recommended for SLE patients who have risk factors for hyperglycemia.

Zeng et al., 2010) Characteristics and risk factors for hyperglycemia in Chinese female patients with systemic lupus erythematosus. Lupus, 2010 Oct;19(11):1344-50. Epub 2010 Aug 6

Autoimmune thyroid disease in SLE

- Autoimmune thyroid disease is common in patients with SLE.
- Antinuclear antibodies are found in the sera of patients with autoimmune thyroid disease, but there is no evidence of autoantibodies binding antigens characteristic of SLE. Autoantibodies to thyroid antigens and overt autoimmune thyroid disease are common in patients with SLE.

Autoimmune thyroid disease in SLE

- The prevalence of of both clinical thyroid disease in SLE (3.9–24%) and the frequency of antithyroid antibodies in SLE (11–51%) have varied widely depending on the study cited.
- SLE had a prevalence of hypothyroidism, but not hyperthyroidism, greater than that of the normal population. The presence of either condition was associated with a higher frequency of both antimicrosomal and antithyroglobulin antibodies (Pyne et al 2002).

Ann Rheum Dis 2002;61:70–7

Autoimmune thyroid disease in SLE

- Thyroid autoantibodies may precede the appearance of clinical autoimmune disease.
- The intermittent biochemical screening of thyroid function in patients with SLE, particularly if they are known to have thyroid antibodies, to identify clinical/subclinical thyroid disease.

Table 1. Prevalence of hypothyroidism among patients with SLE*

Ref. No.	No. of SLE patients	Percent of patients with clinical hypothyroidism
4	69	4.3%
6	300	5.7%
7	63	9.5%
8	129	3.9%
9	45	8.8%
10	70	21.4%
11	332	6.6%

* The prevalence of hypothyroidism in the normal population is 1% [5].

Hypercalcaemia in SLE

- SLE is a very rare cause of hypercalcaemia. It may be associated with lymphadenopathy and pleuritis to constitute a distinct clinical entity described as 'hypercalcaemia-lymphoedema syndrome'. In these cases the pathophysiology of the hypercalcaemia is not completely understood.

Hypercalcaemia in SLE.

- In some cases it is associated with elevated levels of parathyroid-related peptide (PTH-rP). In others the level of PTH-rP is normal, and it has been suggested that autoantibodies may cause hypercalcaemia by activating the PTH receptor.

Home messages

- SLE is characterized by the development of autoantibodies against nuclear antigens.
- SLE is a multi-organ autoimmune disease
- Hormones are implicated in driving this disease
- Nevertheless, therapeutic targeting of hormones is beneficial in SLE, underscoring the contributions of sex in this disease.


Thank You


ANY QUESTION ?